

MAIL STOP APPEAL BRIEF - PATENTS

Atty. Docket No. 0508-1055-2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of

Mohamed CHOKRI et al.

Appeal No. _____

Serial No. 09/304,564

(GROUP 1642)

Filed May 4, 1999

MACROPHAGES, PROCESS FOR PREPARING
THE SAME AND THEIR USE AS ACTIVE
SUBSTANCES OF PHARMACEUTICAL COMPOSITIONS

REQUEST FOR REINSTATEMENT OF APPEAL PURSUANT TO 37 CFR
§1.193(b) (2) (ii)

MAY IT PLEASE YOUR HONORS:

Pursuant to the provisions of 37 CFR §1.193(b) (2) (ii), Appellants hereby request that the present appeal be reinstated. A Supplemental Brief is filed simultaneously herewith. That the conditions of 37 CFR §1.193(b) (2) (ii) are met in this case is evident from the discussion in the accompanying Supplemental Brief.

Respectfully submitted,

YOUNG & THOMPSON

Philip J. Patch Reg. No. 59,696
for

By

Andrew J. Patch
Attorney for Appellants
Registration No. 32,925
745 South 23rd Street
Arlington, VA 22202
Telephone: 703/521-2297

May 19, 2003



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SUPPLEMENTAL APPEAL BRIEF

PURSUANT TO 37 CFR §1.193(b)(2)(ii)

MAY IT PLEASE YOUR HONORS:

The present Supplemental Appeal Brief is filed pursuant to 37 CFR §1.193(b)(2)(ii), and in conjunction with the Request for Reinstatement of the present appeal filed simultaneously herewith, both in response to the recent reopening of prosecution by the Examiner after the appeal had previously been fully briefed.

Although Rule 193(b)(2)(ii) refers to a "supplemental" brief, for the avoidance of confusion we note that the present brief addresses in full the issues now on appeal.

1. Real Party in Interest

The real party in interest in this appeal is the assignee, IDM Immuno-Designed Molecules of Paris, France.

2. Related Appeals and Interferences

Appellant is unaware of any other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

3. Status of Claims

Claims 1 and 2 have been canceled. Claims 3-5 are pending in this application, and the present appeal is taken from the rejection of all of Claims 3-5 in the outstanding Official Action.

4. Status of Amendments

No amendments have been filed subsequent to final rejection of the claims on appeal or subsequent to the reopening of prosecution in the present application.

5. Summary

The invention is a method for treating cancer, which comprises administering both (1) activated macrophages as described for example at page 3, lines 1-14 of the specification, and (2) bispecific antibodies as described for example at page

10, lines 1-11 of the present specification.

In particular, the macrophages administered in the claimed method are characterized by having at least one of the following properties:

(1) their cytotoxic activity without IFN- γ is increased by about 20 to 30% with respect to standard macrophages; (2) their cytotoxic activity with IFN- γ is increased by about 20 to about 40% with respect to standard macrophages; and (3) deactivation of the cytotoxic activity following activation of IFN- γ is such that sixty hours after activation with IFN- γ , the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN- γ activation, with this cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells. (See claim 3 on appeal.)

The bispecific antibodies administered in the claimed method are those which recognize both a) an antigen of these macrophages, and b) an antigen of a tumoral cell to be targeted by these macrophages. (See claim 3 on appeal.)

The macrophages according to the invention are produced by *ex vivo* differentiation of blood monocytes, under culture conditions conferring the improved properties recited in the present claims relative to standard macrophages.

It bears noting that the patentability of the claimed

macrophages *per se*, as well as the patentability of methods for treating cancer using such macrophages, is already established. Specifically, claim 1 of U.S. Patent No. 5,662,899 claims macrophages having the same properties as those of the claims on appeal, and claim 2 of U.S. Patent No. 6,001,351 claims a method for treating cancer comprising administering such macrophages, with the further proviso that the macrophages contain exogenous nucleic acids and/or drugs. Both of these patents issued on ancestor applications of the present application. Copies of U.S. Patents Nos. 5,662,899 and 6,001,351 are attached for ease of reference.

6. Issues

The issues on appeal are as follows:

(1) Whether Claims 3-5 are suitably definite, within the meaning of the second paragraph of 35 USC §112;

(2) Whether Claims 3-5 are anticipated under 35 USC §102(b) by Chokri et al. (Chokri, M et al., Res. Immunol., 143: 95-99, 1992);

(3) Whether Claims 3-5 are anticipated under 35 USC §102(e) by Fanger et al., U.S. Patent No. 5,635,600 or anticipated under 35 USC §102(b) as anticipated by WO 91/05871 (Medarex, Inc. published May 2, 1991); and

(4) Claims 3-5 were rejected under the judicially created obviousness-type double patenting rejection in view of

claims 1 and 12 of United States Patent No. 5,662,899. A Terminal Disclaimer with the appropriate fee has been filed with this Supplemental Appeal Brief to obviate this rejection.

7. Grouping of Claims

The claims are not grouped separately for purposes of the present appeal, with claim 3 being representative.

8. Argument

(1) The Claims are Suitably Definite

The final rejection does not contend that the scope of any of the claims on appeal is in any way unclear. Instead, the final rejection contends that the claims "are broader in scope than what applicant's [sic] appear to regard as their invention."

However, a rejection alleging that the applicant regards the invention as being different or broader from the claims is appropriate only when applicant has stated that the invention is something different from what is defined by the claims. Moreover, the statement must come from somewhere other than in the application as filed (see MPEP § 2172). In fact, absent evidence to the contrary, the claimed invention must be presumed to be that which applicants regard as their invention. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971).

As a result, it is believed that the indefiniteness rejection is fatally flawed for multiple reasons. As noted

above, the claims presumptively set forth what the Applicant regards as his invention. The second paragraph of 35 USC §112 is therefore satisfied when the claims have an understandable scope. As to the claimed invention, the Examiner does not dispute that the claims are of an understandable scope.

The Examiner cites to Paper No. 7 filed January 4, 2001 in support of the indefiniteness rejection. The Examiner contends that appellant has stated that the claimed macrophages are distinguished over the prior art and have the unique properties recited in the claims because of the incubation medium used.

However, nothing in Paper No. 7 suggests that Applicants regard their invention as being narrower than the scope of claim 3 on appeal. Appellants state that "The differences in properties of the macrophages are believed to arise from the different culturing conditions employed. For example, in the Chokri et al. article, the macrophages are cultured in a IMDM medium, whereas in the present specification the macrophages are cultured in the presence of GM-CSF and Vitamin D₃" (Paper No. 7 filed January 4, 2001, pg. 4, first paragraph). Thus, the statement merely serves to explain the present invention by way of example and does not serve to limit the scope of the claims. The present invention is therefore clearly distinguished from the prior art based on the intrinsic properties of the claimed macrophages.

That those properties can be imparted by a range of

processing conditions does not require the processing conditions to be recited in the claims, much less does it evidence any belief by the Applicants that their invention is limited to any particular processing conditions; indeed the language of the claims themselves is conclusively contrary to any such assumption.

It is therefore believed to be apparent that the indefiniteness rejection must be reversed.

(2) Claims 3-5 are not anticipated by Chokri et al.

The final rejection contends that the macrophages of Chokri et al showed an increase in cytotoxic activity within the range of this claimed invention, when they were administered in conjunction with bispecific antibodies.

Indeed, the Chokri et al publication states that the observed increased cytotoxic activity is a result of the macrophages and antibodies in combination with each other (See pg. 97, 2nd column). Moreover, Table I is directed to the "Effect of directing IFN- γ -loaded human RBC with bispecific antibodies (anti-Fc- γ RI/anti-D) on the cytostatic activity of human macrophages towards tumoural cells". Table II is directed to the "Effect of bispecific antibodies on the antitumoral activity of human macrophages *in vitro* and *in vivo*."

However, this stands in contrast to the claimed invention. The claims on appeal require that the macrophages

themselves exhibit the claimed properties. Therefore, even if the Examiner's contentions with respect to Chokri et al. were accurate, they would not support a rejection of any of the claims on appeal.

The impropriety of the anticipation rejection based on Chokri et al. is underscored by the fact that Chokri et al. is a cited reference in both of U.S. Patents Nos. 5,662,8999 and 6,001,351 (see attached copies). Thus, the position of the present Examiner that Chokri et al. teaches the claimed macrophages, in addition to being mistaken on the merits, is also flatly inconsistent with the allowance of claim 1 in U.S. Patent No. 5,662,899, which claims macrophages having the identical properties.

The implicit contention of the present Examiner, in rejecting the claims on appeal based on the previously-considered Chokri et al. article, is therefore that the Examiner who acted on the attached U.S. Patents Nos. 5,662,899 and 6,001,351 did not do her job correctly, and in fact that at least claims 1 of U.S. Patent No. 5,662,899 is invalid based on prior art of record in that patent. Again, in addition to the substantive impropriety of that position, as discussed above, the present Examiner's position would seem to run afoul of the restrictions imposed by MPEP §1701.

It is therefore believed also to be apparent that the rejection based on Chokri et al is improper and must be reversed.

(3) Claims 3-5 are not anticipated by Fanger or Medaraex

The rejections based on Fanger and Medaraex are based on wholly unsupported contentions by the Examiner that the macrophages mentioned in those references are the same as those required by the claims on appeal. Again, we point out that the position of the present Examiner would seriously disparage the validity of at least claim 1 of the attached U.S. Patent No. 5,662,899, in violation of MPEP §1701, given that claim 1 of the '899 patent specifically claims macrophages having the same intrinsic properties called for in the claims on appeal.

In fact, however, the macrophages used in the claimed methods are distinctly different than those of the Fanger and Medarex references. The Examiner tacitly acknowledges the shortcomings of these references relative to the claims on appeal, by failing to identify where, in either reference, any of the claimed macrophage properties are disclosed.

Instead, it appears that the entire basis for the Examiner's reliance on these references relative to the claimed macrophages is her allegation, at pp. 4-5 of Paper No. 8, that "[t]he macrophages [of the applied references] may be treated with interferon-gamma." Using only that slender and insufficient reed, the Examiner proceeds to assume that the claimed macrophages and those of the references are "the same," and seeks to impose on Applicants an entirely inappropriate burden of

disproving these unwarranted assumptions.

However, the present specification itself teaches, and the claims on appeal require, that the recited macrophages display markedly superior cytotoxic activity relative to standard macrophages, whether they are activated with or without IFN- γ . Therefore, by definition, mere treatment with interferon gamma is insufficient to produce macrophages as required by the present claims.

It further bears noting that Fanger et al does not teach properties of macrophages by themselves, but rather only in conjunction with bispecific antibodies. Thus, the reference does not teach increasing the macrophage's cytotoxicity without the bispecific antibody coating. Macrophages that are, by themselves, 20 to 30% more cytotoxic than standard macrophages are nowhere taught or suggested by Fanger et al.

Medaraex describes cultivating monocytes in a culture medium in order to differentiate the monocytes into macrophages. However, nothing in this reference teaches producing macrophages in such a way as to increase the cytotoxicity of these macrophages by 20 to 30% over standard macrophages.

Further evidence that the Medarex macrophages do not respond to the requirements of claim 3 on appeal is found in part (a) of claim 18 of Medarex, which requires "an effector cell expressing high affinity Fc- γ receptor." An effector cell (i.e., macrophage), expressing Fc- γ receptors indicates the

effector cell is cytotoxic. It is conventional for a macrophage to express $\text{Fc-}\gamma$ receptors, but this applied reference does not teach or suggest macrophages with an increase in cytotoxicity compared to standard macrophages (which may be indicated by an increased expression of $\text{Fc-}\gamma$ receptors). It merely describes an effector cell with cytotoxic activity as a potential host to bispecific antibodies.

Conclusion

From the above discussion, it is believed to be apparent that the final rejection of claims 3-5 cannot properly be affirmed as to any of the grounds of rejection on appeal, but instead must be reversed. Such action is accordingly respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

Philip W. Patch Reg. No. 50,696

By

for

Andrew J. Patch
Attorney for Appellants
Registration No. 32,925
745 South 23rd Street
Arlington, VA 22202
Telephone: 703/521-2297

May 19, 2003

9. Appendix

The claims on appeal:

3. A method for treating cancer, comprising administering to a patient in need of said treatment

(i) macrophages having at least one of the following properties:

- their cytotoxic activity without IFN- γ is increased by about 20 to 30% with respect to standard macrophages;

- their cytotoxic activity with IFN- γ is increased by about 20 to about 40% with respect to standard macrophages;

- deactivation of the cytotoxic activity following activation of IFN- γ is such that sixty hours after activation with IFN- γ , the residual cytotoxic activity is at least 30% of the maximum cytotoxic activity presented by the macrophages due to IFN- γ activation, with said cytotoxic activity being measured as a percentage of the inhibition of 3-H thymidine incorporation by target tumoral cells, particularly U 937 cells; and

(ii) bispecific antibodies which recognize both a) an antigen of said macrophages, and b) an antigen of a tumoral cell to be targeted by said macrophages.

4. The method according to claim 3, wherein the macrophages are injected at the same time as the bispecific antibodies.

5. The method according to claim 3, wherein the bispecific antibodies are preincubated with macrophages before injection.